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VB

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 09/576,951 | 05/24/00 | MOLNAR-KIMBER K | A-7733 |

HM22/0807
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| EXAMINER | |
|---|---|
| CEPERLEY,M | |
| **ART UNIT** | **PAPER NUMBER** |
| 1641 | 8 |

**DATE MAILED:** 08/07/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/576,951 | Applicant(s) MOLNAR-KIMBER ET AL. | |
|---|---|---|---|
| | Examiner Mary E. (Molly) Ceperley | Art Unit 1641 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *33-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4 and 7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Ex parte Erlich Decision

1. The four forms PTO-1449 which were submitted by applicants are attached to this Office action. The references which have been initialed have been considered by the examiner. However, the uninitialed references are not in the file of this application nor in any of the parent applications and have not been considered by the examiner. Upon receipt of copies of these missing references, the examiner will consider them and provide applicants with another copy of initialed forms PTO-1449 with the next Office action.

2. The examiner has noted applicants' reference to EP 693,132 B1, cited in the Preliminary Amendment (equivalent to WO94/24304, of record on PTO-1449), which is drawn to 28- and 40- immunoconjugates of rapamycin which correspond to the renumbered 31- and 42- immunoconjugates of the instant claims.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

4. Claims 33-40 are rejected under 35 USC 112, second paragraph, as being indefinite for the following reasons.

a) In claim 33, it is unclear what is meant by the term "a rapamycin" since "rapamycin" is a single compound and not a class of compounds.

b) In claim 33, it is unclear what is meant by a "linking group" since it is not specified what type of chemical moiety this group is and what it "links" to.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 33-40 are rejected under 35 USC 103(a) as being obvious over each of ***(1)*** Stella et al (U.S. 4,650,803), Failli et al (A) (U.S. 5,177,203), Kao et al (U.S. 5,118,678), Kao (U.S. 5,294,447), Caufield (U.S. 5,118,677), Amer. Home Prods. (WO 92/05179), or Failli et al (B) (U.S. 5,130,307) taken in combination with each of references ***(b)*** Sevier et al (Clinical Chemistry, 27/11, 1797-1806 (1981); Yelton et al (American Scientist, 68, 510-516 (1980)); or Campbell (Monoclonal Antibody and Immunosensor Technology, Chapter 1, Elsevier (1991)).

Each of references ***(1)*** describes pharmaceutically active rapamycin derivatives which are substituted at the positions which correspond to either the 42- or 31-position of the rapamycin compounds as depicted in structure I of page 3 of the instant application. See Stella et al: Figure 1; col. 1, lines 49-68; Failli et al (A): structure (I); Kao et al: col. 1, line 45 – col. 2, line 34; Kao: abstract; Caufield: abstract; Amer. Home Prods.: title and abstract; Failli et al (B): abstract. These references establish that rapamycin 42- or 31-substituted rapamycin derivatives are well known pharmaceutically active agents. These references do not describe the production of antibodies specific for these pharmaceutical agents.

References ***(2)*** establish that it is well known in the art that monoclonal antibodies to an extremely wide variety of known antigens may be prepared using conventional immunogenic hapten-carrier conjugates. See Sevier et al, the entire article, in particular, Table 2; Yelton et al: the entire article; Campbell: the entire article, in particular, section 1.17.6.

Given the fact that 42- and 31- substituted rapamycin derivatives are well known drugs (references ***(1)***), it is considered to be well within the level of skill in the art and therefore obvious to substitute these derivatives as haptens in a conventional method of preparing immunogenic conjugates as described in references ***(2)***, as claimed, with the expectation of conventionally using these immunogens to obtain similarly useful antibodies specific for the 42- and 31-substituted rapamycin epitopes. See *Ex parte Erlich,* 3 USPQ2d 1011, in particular, page 1015, column 1.

7. Claims 33-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over each of references ***(1)*** of paragraph 6. above taken in combination with each of references ***(2)*** of paragraph 6. above and further in combination with Niwa et al (U.S. 5,532,137).

References ***(1)*** and ***(2)*** are applied for the reason stated in paragraph 6. above.

Niwa et al is applied for its description of the preparation of immunogens which use FR-900506, a macrocyclic structure very similar to rapamycin, as a hapten. See the structure of col. 7 where the point of attachment of the linker is at a position which

corresponds to the 42-position of the instant rapamycin derivative and the monoclonal antibody production of Example 2.

Given the fact that 42- and 31- substituted rapamycin derivatives are well known drugs (references ***(1)***), it is considered to be well within the level of skill in the art and therefore obvious to substitute these derivatives as haptens in a conventional method of preparing immunogenic conjugates as described in references ***(2)***, as claimed, with the expectation of conventionally using these immunogens to obtain similarly useful antibodies specific for the 42- and 31-substituted rapamycin epitopes. This is particularly true in view of the further teaching of Niwa et al that antibodies to very structurally similar macrocyclic compounds can be prepared using 42-substituted hapten/carrier conjugates.

Applicants' argument (filed August 30, 2000) that it was unpredictable that antibodies could be generated against rapamycin even though it was known that antibodies could be generated against the structurally similar FR-900506 compound of Niwa et al is not persuasive. Although the mechanism of pharmaceutical action may be different for rapamycin derivatives and the FR-900506 derivatives of Niwa et al (pages 4-6 of the August 30, 2000 response), the prior art cited by applicants in their response does ***not*** support the position that it would be unexpected that antibodies to rapamycin derivatives could be prepared. The cited prior art, on the contrary, relates only to the ***general immunosuppressive effect*** of rapamycin and not to the production of antibodies ***specific for*** rapamycin.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary E. (Molly) Ceperley whose telephone number is (703) 308-4239. The examiner can normally be reached from 8 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-7230.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

August 6, 2001

Mary E. Ceperley
Primary Examiner
Art Unit 1641